REMARKS

Applicants note that the correspondence address was changed for this application in the papers submitted on February 26, 2008 and request the record be corrected to reflect this change. All future correspondence should be directed to the address associated with customer number 23463 (11 South Meridian St., Indianapolis, IN 46204-3535).

Applicants have amended claim 15 to specify that the ERK8 peptides to be detected and monitored are those that bind to antibodies that specifically bind to the peptide to SEQ ID NO: 1. Support for the amendment is found on page 12, lines 6-9. Claim 15 is further amended to specify a step of initially contacting the cancer cells with the anti-cancer agent and to further state that increasing the ERK8 levels after the cells are treated with the anti-cancer agent (i.e., relative to the levels prior to said treatment) indicates the efficacy of the treatment. New claim 21 specifies that the cancer cells are contacted *in vivo* with the anti-cancer agent whereas the monitoring of ERK levels is conducted *in vitro* on a recovered sample. Support for new claim 21 is found on page 10, lines 14-15 and page 11, lines 26-31. New claim 23 has been added and is directed to a further embodiment wherein the efficacy of an anti-cancer therapy is assessed by monitoring the levels of a peptide comprising the amino acid sequence of SEQ ID NO: 1. Support for new claim 23 is found in original claim 15 and on page 8, lines 4-5. New claims 22 and 24 specify that the cancer cell is a breast cancer cell. Support for new claims 22 and 24 is found on page 9, lines 5-7.

Claims 15-18 stand rejected under 35 USC 112, first paragraph for lack of written description. Applicants respectfully traverse the Examiner's rejection but in an effort to expedite the prosecution of the present application, applicants have amended claim 15 to further specify the identity of the peptides to be detected and monitored in accordance with the present invention. These include peptides that specifically bind to an antibody raised against the amino acid sequence of SEQ ID NO: 1 (ERK8). Written support for claim 15 as amended is provided at page 8, lines 4-5 and 9-10, page 11, lines 20-30 and page 12, lines 6-9. Applicants note that the preparation of antibodies to specific antigens is well known to those skilled in that art. Accordingly, applicants respectfully submit that claim 15 fully complies with the written

description requirement of 35 USC 112, and applicants request the withdrawal of the rejection of claims 15-18 for lack of a written description.

Claims 15-18 stand rejected under 35 USC 112, second paragraph, for indefiniteness for the omission of essential elements. More particularly, the Examiner contends claim 15 fails to disclose a specific level of ERK8 that is associated with beneficial treatment of cancer cells. Applicants respectfully traverse this rejection.

Applicants respectfully submit that one of ordinary skill in the art will appreciate that the relevant levels of ERK8 will vary from patient to patient and between estrogen responsive cancer cell types. However, as noted in the specification, if the ERK8 levels of an estrogen responsive cancer are increased as a result of the anti-cancer therapy, this alone represents a beneficial result. Such a result is sufficient to establish that the anti-cancer therapy has some level of effectiveness as a treatment. This is all that is required by the claim. Obviously, a greater the increase in the levels of ERK8 that are detected after treatment with the anti-cancer agent, relative to the levels detected prior to the treatment, is anticipated to be correlated with a higher level of effectiveness of the therapy.

In an effort to address the Examiner's concerns regarding the definiteness of the claims, and to advance the prosecution of the present invention, applicants have amended claim 15 to further state the temporal relationship between administering the anti-cancer agent and the monitoring of the ERK8 levels. More particularly, the claims have been revised to state, "wherein an increase in said ERK8 levels after said contact with said agent indicates efficacy for said anti-cancer agent."

Applicants respectfully submit that one of ordinary skill in the art would readily comprehend whether or not their acts would fall within the scope of the claims. 35 USC 112, second paragraph requires nothing more. Accordingly, applicants respectfully request the withdrawal of the rejection of claims 15-18 for indefiniteness.

Claims 15, 16 and 18 stand rejected under 35 USC 102(e) as being anticipated by US patent no. 6,759,221. Applicants respectfully traverse this rejection.

The '221 patent discloses a novel gene sequence and its deduced amino acid sequence. The sequence of the deduced polypeptide has an amino acid sequence similar to SEQ ID NO: 1 of the present invention, and the '221 patentees propose that their disclosed polypeptide has kinase activity. The patentees then further speculate that

> Inhibition or over stimulation of the activity of kinases involved in signaling pathways associated with cellular growth can lead to perturbed cellular growth, which can in turn lead to cellular growth-related disorders. As used herein, a "cellular growth-related disorder" includes a disorder, disease, or condition characterized by a deregulation, e.g., an up-regulation or a down-regulation, of cellular growth.

The '221 patentee's then provide a long laundry list of diseases and disorders that can be diagnosed and treated through the use of modulators of the disclosed presumptive kinase (see column 10, lines 16-54. However, the reference fails to teach that monitoring the levels of ERK8, can be used to determine the effectiveness of an estrogen responsive anti-cancer therapy. At best the '221 patent teaches a method of diagnosing a disease by monitoring the concentration of an ERK8-like peptide. The reference is devoid of any teaching with regards to a method of contacting cancer cells with an anti-cancer agent **and then** subsequently monitoring the levels of ERK8 in said contacted cells to determine the efficacy of the anti-cancer therapeutic itself. the patent only discloses directly targeting kinases for modification of their expression.

Applicants have discovered that ERK8 expression in humans is correlated with enhanced destruction of ERα. ERα regulates the expression of genes involved in growth and proliferation. ERα is believed to play a key role during the development of breast, endometrial and other estrogen dependent cancers in part due to the fact that the cellular response to estrogens *in vivo* is ERα-limited. Applicants have discovered that decreased levels of ERK8 are associated with the development/existence of estrogen responsive cancer cells. It is this discovery that led to the present invention which is directed to monitoring the effectiveness of an anti-cancer agent for treating estrogen responsive cancers, by detecting the level of ERK8 after administering the anti-cancer therapy.

The '221 patent only discloses a broad generalized teaching that "kinase" activity is associated with "a cellular growth-related disorder". At best this reference merely provides an invitation to experiment and fails to provide any motivation to do what applicants have done and

now claim as their invention. In particular, the '221 patent is devoid of any teaching that the monitoring of ERK8 levels would be relevant for a specific subset of cancer cells, specifically estrogen responsive cancers. Absent this specific teaching, it is unlikely one would be able to interpret meaningful results by monitoring ERK8 levels on randomly selected cancer cells.

It is well settled that in order for a single reference to anticipate a claim under 35 U.S.C. § 102, that reference must include, either expressly or inherently, each and every element, i.e., limitation, of the claim. See, for example, In re Verdegaal, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). There is simply no teaching in the '221 patent that the efficacy of an anti-estrogen responsive cancer treatment could be determined by monitoring ERK8 levels in the estrogen responsive cancer cells contacted with the anti-cancer agent. The reference fails to reach the monitoring of ERK8 levels in conjunction with the administration of a specific anti-cancer agent.

Accordingly applicants respectfully submit the '221 patent fails to anticipate the invention of claims 15, 16 and 18 and applicants respectfully request the withdrawal of the rejection of the claims as being anticipated by that reference.

Claims 15-18 stand rejected under 35 USC 103(a) as being obvious over the teachings of US patent no. 6,759,221 further in view of Inoue et al. Applicants respectfully traverse this rejection.

As noted above the primary reference fails to teach or suggest a method of determining an anti-cancer's effectiveness against an estrogen responsive cancer cell. Applicants respectfully submit that while the '221 patentees suggest that kinase levels may be used as markers for "monitoring the effectiveness of treatment of a subject with an agent" the teaching is too broad and generalized to provide an effective teaching that would lead on of ordinary skill in the art to the present invention. In disclosing the possibility of using kinase expression as a "marker", the '221 patent fails to identify with any specificity which disease/disorder such monitoring would be effective. The disclosure that "kinase" activity can be associated with "a cellular growth-related disorder" may provide an invitation to experiment, but the reference fails to provide any specific teaching or guidance for selecting one of the many different species of disorders encompassed by the phrase "a cellular growth-related disorder". The fact that a claimed species or subgenus is

encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird,* 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994).

Furthermore, applicants respectfully submit that cancer diagnostics represent an unpredictable field of technology. Accordingly, one of ordinary skill in the art reading the '221 patent disclosure would not accept the broad generalization that all kinases are associated with cellular growth-related disorders. Furthermore, such a broad disclosure would not have motivated one to modify the disclosed invention of the '221 patent to generate the specific method as claimed in the present invention. Applicants respectfully submit the Examiner has failed to establish why one of ordinary skill in the art would select estrogen responsive cancer cells as the specific disease state to monitor ERK8 levels as a determinant of the efficacy of an anti-cancer agent against that specific type of cancer.

The cited secondary reference fails to supplement the inadequacies of the primary reference in terms of its failure to teach or suggest the specific claimed method of monitoring ERK8 levels in estrogen responsive cancer cells as a measure of the effectiveness of an anti-cancer agent against such cells. Inoue et al does discuss estrogen responsive cancer cell lines and notes that "ERα is a primary determinant in the anti-hormone therapy of breast cancer..." (page 175, second column), but the reference fails to make any mention regarding ERK8 expression. Instead, the reference discloses a wide array of proteins that are upregulated in estrogen responsive cancer cells relative to normal breast cells. Inoue et al fails to identify ERK8 as a protein of any relevance in estrogen responsive cancer cells.

Applicants respectfully submit that absent applicants disclosed discovery that ERK8 levels are found to be low in estrogen responsive cancer cells there is simply no objective reason for combining the teaching of Inoue et al with the teaching of the '221 patent. Applicants respectfully submit the combination is improper and that Examiner has failed to establish a *prima facie* case of obviousness.

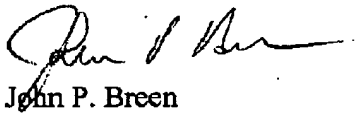
Furthermore, applicants respectfully submit that even when the teachings of Inoue and the '221 patent are considered for all their combined teaching, the references still fail to teach or suggest the present invention. There is simply no teaching or suggestion that ERK8 levels would have particular relevance for monitoring the therapeutic effectiveness of an anti-cancer agent against estrogen responsive cancer cells. That important link only comes from applicant's

discovery that ERK8 enhances hormone-dependent destruction of ERα and that low levels of ERK8 are associated with estrogen responsive cancers, and the aggressiveness of the particular estrogen responsive cancer cell.

The present claimed invention, as amended herein, is believed to be patentable over the teachings of the '221 patent and Inoue et al. Accordingly, applicants request the withdrawal of the rejection of claim 15-18 for obviousness.

The foregoing claim amendments and remarks are believed to fully respond to the Examiner's rejections and the claims are believed to be in condition for allowance. Applicants respectfully request allowance of the claims, and passage of the application to issuance. If any further discussion of this matter would speed prosecution of this application, the Examiner is invited to call the undersigned at (434) 220-2866.

Respectfully submitted,



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